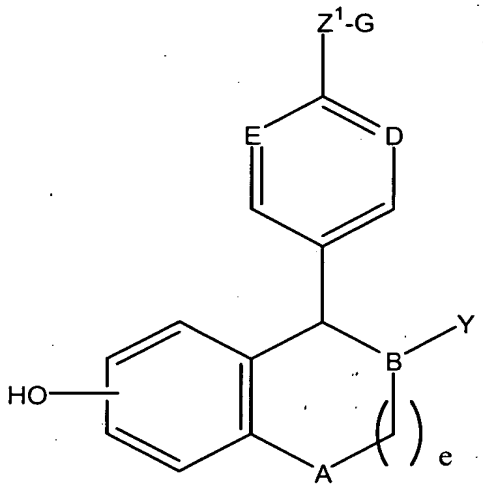
CLAIMS

What is claimed is:

1. A method of treating joint pain or improving sleep in a patient, the method comprising administering to said patient in need thereof a therapeutically effective amount of a SERM of formula (I):



(I)

wherein:

A is selected from CH_2 and NR;

B, D and E are independently selected from CH and N;

Y is

(a) phenyl, optionally substituted with 1-3 substituents independently selected from R^4;

(b) naphthyl, optionally substituted with 1-3 substituents independently selected from R^4;

(c) C_3-C_8 cycloalkyl, optionally substituted with 1-2 substituents independently selected from R^4;

(d) C_3-C_8 cycloalkenyl, optionally substituted with 1-2 substituents independently selected from R^4;

(e) a five membered heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NR^2- and -$S(O)_n$-, optionally substituted with 1-3 substituents independently selected from R^4;

(f) a six membered heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NR^2- and -$S(O)_n$- optionally substituted with 1-3 substituents independently selected from R^4; or

(g) a bicyclic ring system consisting of a five or six membered heterocyclic ring fused to a phenyl ring, said heterocyclic ring containing up to two heteroatoms selected from the group consisting of -O-, -NR^2- and -$S(O)_n$-, optionally substituted with 1-3 substituents independently selected from R^4;

Z^1 is

(a) -$(CH_2)_p$ $W(CH_2)_q$-;

(b) -$O(CH_2)_p$ CR^5R^6-;

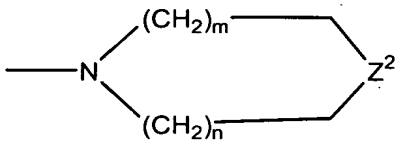
(c) -$O(CH_2)_pW(CH_2)_q$-;

(d) -$OCHR^2CHR^3$-; or

(e) -$SCHR^2CHR^3$-;

G is

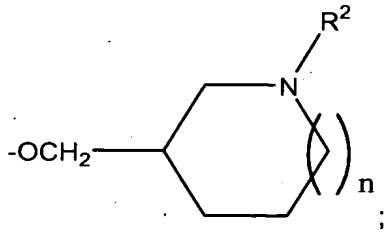
(a) -NR^7R^8;

(b) 

wherein n is 0, 1 or 2; m is 1, 2 or 3; Z^2 is -NH-, -O-, -S-, or -CH_2-; optionally fused on adjacent carbon atoms with one or two phenyl rings and, optionally independently substituted on carbon with one to three substituents and, optionally, independently on nitrogen with a chemically suitable substituent selected from R^4; or

(c) a bicyclic amine containing five to twelve carbon atoms, either bridged or fused and optionally substituted with 1-3 substituents independently selected from R^4; or

Z^1 and G in combination may be



;

W is

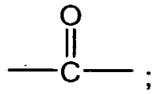
(a) $-CH_2-$;

(b) -CH=CH-;

(c) -O-;

(d) $-NR^2-$;

(e) $-S(O)_n-$;

(f)  ;

(g) $-CR^2(OH)-$;

(h) $-CONR^2-$;

(i) $-NR^2CO-$;

(j)  ; or

(k) $-C\equiv C-$;

R is hydrogen or C_1-C_6 alkyl;

R^2 and R^3 are independently

(a) hydrogen; or

(b) C_1-C_4 alkyl;

R^4 is

(a) hydrogen;

(b) halogen;

(c) C_1-C_6 alkyl;

(d) C_1-C_4 alkoxy;

(e) C_1-C_4 acyloxy;

(f) C_1-C_4 alkylthio;

(g) C_1-C_4 alkylsulfinyl;

(h) C_1-C_4 alkylsulfonyl;

(i) hydroxy (C_1-C_4)alkyl;

(j) aryl (C_1-C_4)alkyl;

(k) -CO_2H;

(l) -CN;

(m) -CONHOR;

(n) -SO_2NHR;

(o) -NH_2;

(p) C_1-C_4 alkylamino;

(q) C_1-C_4 dialkylamino;

(r) -$NHSO_2$R;

(s) -NO_2;

(t) -aryl; or

(u) -OH;

R^5 and R^6 are independently C_1-C_8 alkyl or together form a C_3-C_{10} carbocyclic ring;

R^7 and R^8 are independently

(a) phenyl;

(b) a C_3-C_{10} carbocyclic ring, saturated or unsaturated;

(c) a C_3-C_{10} heterocyclic ring containing up to two heteroatoms, selected from -O-, -N- and -S-;

(d) H;

(e) C_1-C_6 alkyl; or

(f) form a 3 to 8 membered nitrogen containing ring with R^5 or R^6;

R^7 and R^8 in either linear or ring form may optionally be substituted with up to three substituents independently selected from C_1-C_6 alkyl, halogen, alkoxy, hydroxy and carboxy;

a ring formed by R^7 and R^8 may be optionally fused to a phenyl ring;

e is 0, 1 or 2;

m is 1, 2 or 3;

n is 0, 1 or 2;

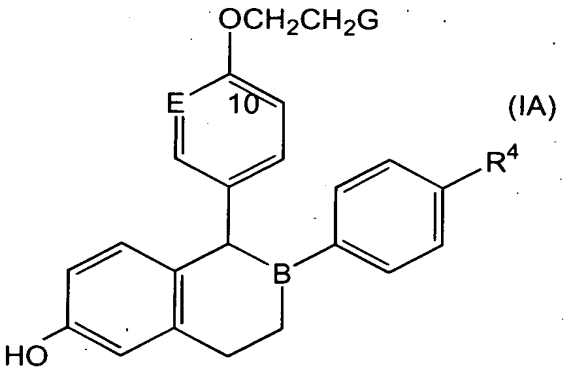
p is 0, 1, 2 or 3;

q is 0, 1, 2 or 3;

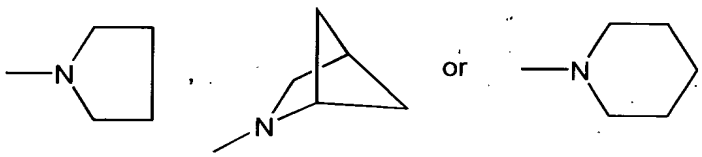
or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof; and provided

that said joint pain is not joint pain resulting from osteoarthritis or rheumatoid arthritis.

2. The method of claim 1 wherein the SERM is a compound of formula (IA)



wherein G is



;

R^4 is H, OH, F, or Cl; and B and E are independently selected from CH and N or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

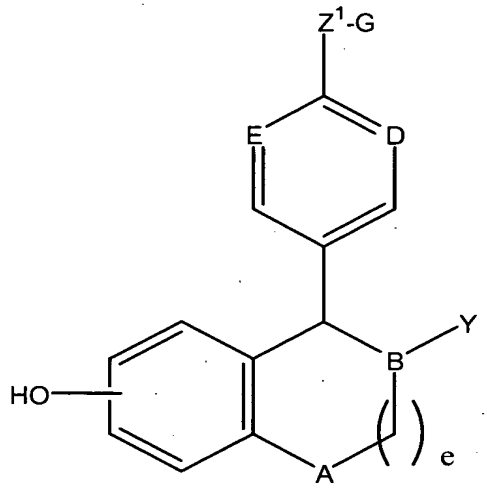
3. The method of claim 1 wherein the SERM is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol or an optical or geometric isomer thereof; a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

4. The method of claim 3 wherein the SERM is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol, D-tartrate salt.

5. The method of any one of claims 1-4 wherein the method is the method of treating joint pain.

6. The method of any one of claims 1-4 wherein the method is the method of improving sleep.

7. A method of treating joint pain in a patient, the method comprising administering to said patient in need thereof a therapeutically effective amount of a first compound, said first compound being a SERM of formula (I):



(I)

wherein:

A is selected from CH_2 and NR;

B, D and E are independently selected from CH and N;

Y is

(a) phenyl, optionally substituted with 1-3 substituents independently selected from R^4;

(b) naphthyl, optionally substituted with 1-3 substituents independently selected from R^4;

(c) C_3-C_8 cycloalkyl, optionally substituted with 1-2 substituents independently selected from R^4;

(d) C_3-C_8 cycloalkenyl, optionally substituted with 1-2 substituents independently selected from R^4;

(e) a five membered heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NR^2- and -$S(O)_n$-, optionally substituted with 1-3 substituents independently selected from R^4;

(f) a six membered heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NR^2- and -$S(O)_n$- optionally substituted with 1-3 substituents independently selected from R^4; or

(g) a bicyclic ring system consisting of a five or six membered heterocyclic ring fused to a phenyl ring, said heterocyclic ring containing up to two heteroatoms selected from the group consisting of -O-, -NR^2- and -$S(O)_n$-, optionally substituted with 1-3 substituents independently selected from R^4;

Z^1 is

(a) -$(CH_2)_p$ $W(CH_2)_q$-;

(b) -$O(CH_2)_p$ CR^5R^6-;

(c) -$O(CH_2)_pW(CH_2)_q$-;

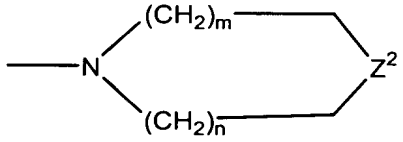
(d) -$OCHR^2CHR^3$-; or

(e) -$SCHR^2CHR^3$-;

G is

(a) -NR^7R^8;

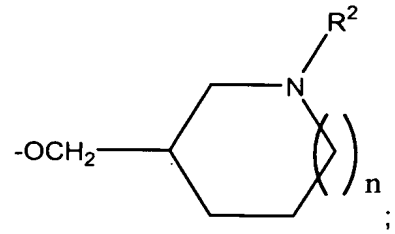
(b)



wherein n is 0, 1 or 2; m is 1, 2 or 3; Z^2 is -NH-, -O-, -S-, or -CH_2-; optionally fused on adjacent carbon atoms with one or two phenyl rings and, optionally independently substituted on carbon with one to three substituents and, optionally, independently on nitrogen with a chemically suitable substituent selected from R^4; or

(c) a bicyclic amine containing five to twelve carbon atoms, either bridged or fused and optionally substituted with 1-3 substituents independently selected from R^4; or

Z^1 and G in combination may be



;

W is

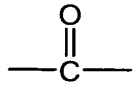
(a) $-CH_2-$;

(b) $-CH=CH-$;

(c) $-O-$;

(d) $-NR^2-$;

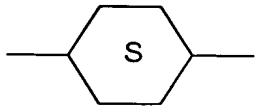
(e) $-S(O)_n-$;

(f)  ;

(g) $-CR^2(OH)-$;

(h) $-CONR^2-$;

(i) $-NR^2CO-$;

(j)  ; or

(k) $-C\equiv C-$;

R is hydrogen or C_1-C_6 alkyl;

R^2 and R^3 are independently

(a) hydrogen; or

(b) C_1-C_4 alkyl;

R^4 is

(a) hydrogen;

(b) halogen;

(c) C_1-C_6 alkyl;

(d) C_1-C_4 alkoxy;

(e) C_1-C_4 acyloxy;

(f) C_1-C_4 alkylthio;

(g) C_1-C_4 alkylsulfinyl;

(h) C_1-C_4 alkylsulfonyl;

(i) hydroxy (C_1-C_4)alkyl;

(j) aryl (C_1-C_4)alkyl;

(k) -CO_2H;

(l) -CN;

(m) -CONHOR;

(n) -SO_2NHR;

(o) -NH_2;

(p) C_1-C_4 alkylamino;

(q) C_1-C_4 dialkylamino;

(r) -$NHSO_2R$;

(s) -NO_2;

(t) -aryl; or

(u) -OH;

R^5 and R^6 are independently C_1-C_8 alkyl or together form a C_3-C_{10} carbocyclic ring;

R^7 and R^8 are independently

(a) phenyl;

(b) a C_3-C_{10} carbocyclic ring, saturated or unsaturated;

(c) a C_3-C_{10} heterocyclic ring containing up to two heteroatoms, selected from -O-, -N- and -S-;

(d) H;

(e) C_1-C_6 alkyl; or

(f) form a 3 to 8 membered nitrogen containing ring with R^5 or R^6;

R^7 and R^8 in either linear or ring form may optionally be substituted with up to three substituents independently selected from C_1-C_6 alkyl, halogen, alkoxy, hydroxy and carboxy;

a ring formed by R^7 and R^8 may be optionally fused to a phenyl ring;

e is 0, 1 or 2;

m is 1, 2 or 3;

n is 0, 1 or 2;

p is 0, 1, 2 or 3;

q is 0, 1, 2 or 3;

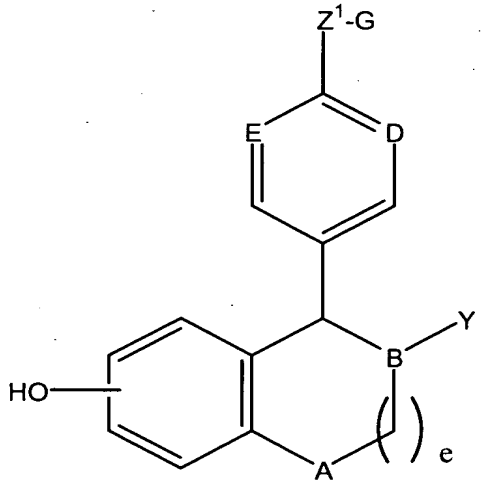
or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof; and

a therapeutically effective amount of a second compound, said second compound selected from the group consisting of acetominophen, aspirin, ibuprofen, naproxen, ketoprofen, nabumetone, etodolac, salsalate, sulindac, diclofenac, tolmetin, flurbiprofen, piroxicam, fenoprofen, indomethacin, meclofenamate, oxaprozin, diflunisal, ketorolac, celecoxib, rofecoxib, valdecoxib, etoricoxib, hyaluronic acid, glucosamine, chondroitin and capsaicin; provided that said joint pain is not joint pain resulting from osteoarthritis or rheumatoid arthritis.

8. The method of claim 7 wherein the first compound is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol, D-tartrate salt.

9. The method of claim 8 wherein the second compound is celecoxib, rofecoxib, valdecoxib or etoricoxib.

10. A method of improving sleep in a patient, the method comprising administering to said patient in need thereof a therapeutically effective amount of a first compound, said first compound being a SERM of formula (I):



(I)

wherein:

A is selected from CH_2 and NR;

B, D and E are independently selected from CH and N;

Y is

(a) phenyl, optionally substituted with 1-3 substituents independently selected from R^4;

(b) naphthyl, optionally substituted with 1-3 substituents independently selected from R^4;

(c) C_3-C_8 cycloalkyl, optionally substituted with 1-2 substituents independently selected from R^4;

(d) C_3-C_8 cycloalkenyl, optionally substituted with 1-2 substituents independently selected from R^4;

(e) a five membered heterocycle containing up to two heteroatoms selected from the group consisting of -O-, $-NR^2-$ and $-S(O)_n-$, optionally substituted with 1-3 substituents independently selected from R^4;

(f) a six membered heterocycle containing up to two heteroatoms selected from the group consisting of -O-, $-NR^2-$ and $-S(O)_n-$ optionally substituted with 1-3 substituents independently selected from R^4; or

(g) a bicyclic ring system consisting of a five or six membered heterocyclic ring fused to a phenyl ring, said heterocyclic ring containing up to two heteroatoms selected from the group consisting of -O-, $-NR^2-$ and $-S(O)_n-$, optionally substituted with 1-3 substituents independently selected from R^4;

Z^1 is

(a) $-(CH_2)_p W(CH_2)_q-$;

(b) $-O(CH_2)_p CR^5R^6-$;

(c) $-O(CH_2)_pW(CH_2)_q-$;

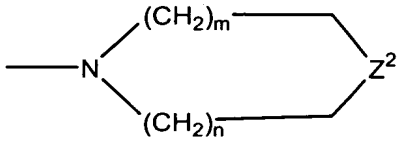
(d) $-OCHR^2CHR^3-$; or

(e) $-SCHR^2CHR^3-$;

G is

(a) $-NR^7R^8$;

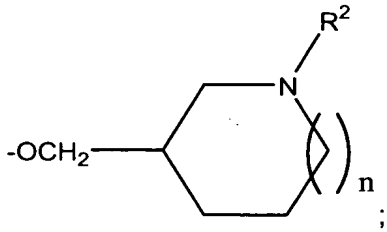
(b)



wherein n is 0, 1 or 2; m is 1, 2 or 3; Z^2 is -NH-, -O-, -S-, or $-CH_2-$; optionally fused on adjacent carbon atoms with one or two phenyl rings and, optionally independently substituted on carbon with one to three substituents and, optionally, independently on nitrogen with a chemically suitable substituent selected from R^4; or

(c) a bicyclic amine containing five to twelve carbon atoms, either bridged or fused and optionally substituted with 1-3 substituents independently selected from R^4; or

Z^1 and G in combination may be



;

W is

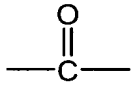
(a) $-CH_2-$;

(b) -CH=CH-;

(c) -O-;

(d) $-NR^2-$;

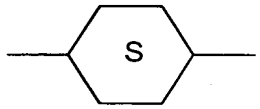
(e) $-S(O)_n-$;

(f)  ;

(g) $-CR^2(OH)-$;

(h) $-CONR^2-$;

(i) $-NR^2CO-$;

(j)  ; or

(k) $-C\equiv C-$;

R is hydrogen or C_1-C_6 alkyl;

R^2 and R^3 are independently

(a) hydrogen; or

(b) C_1-C_4 alkyl;

R^4 is

(a) hydrogen;

(b) halogen;

(c) C_1-C_6 alkyl;

(d) C_1-C_4 alkoxy;

(e) C_1-C_4 acyloxy;

(f) C_1-C_4 alkylthio;

(g) C_1-C_4 alkylsulfinyl;

(h) C_1-C_4 alkylsulfonyl;

(i) hydroxy (C_1-C_4)alkyl;

(j) aryl (C_1-C_4)alkyl;

(k) $-CO_2H$;

(l) -CN;

(m) -CONHOR;

(n) $-SO_2NHR$;

(o) $-NH_2$;

(p) C_1-C_4 alkylamino;

(q) C_1-C_4 dialkylamino;

(r) $-NHSO_2R$;

(s) $-NO_2$;

(t) -aryl; or

(u) -OH;

R^5 and R^6 are independently C_1-C_8 alkyl or together form a C_3-C_{10} carbocyclic ring;

R^7 and R^8 are independently

(a) phenyl;

(b) a C_3-C_{10} carbocyclic ring, saturated or unsaturated;

(c) a C_3-C_{10} heterocyclic ring containing up to two heteroatoms, selected from -O-, -N- and -S-;

(d) H;

(e) C_1-C_6 alkyl; or

(f) form a 3 to 8 membered nitrogen containing ring with R^5 or R^6;

R^7 and R^8 in either linear or ring form may optionally be substituted with up to three substituents independently selected from C_1-C_6 alkyl, halogen, alkoxy, hydroxy and carboxy;

a ring formed by R^7 and R^8 may be optionally fused to a phenyl ring;

e is 0, 1 or 2;

m is 1, 2 or 3;

n is 0, 1 or 2;

p is 0, 1, 2 or 3;

q is 0, 1, 2 or 3;

or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof; and

a therapeutically effective amount of a second compound, said second compound being selected from the group consisting of adinazolam, allobarbital, alonimid, alprazolam, amitryptiline, amobarbital, amoxapine, bentazepam, benzoctamine, bromocriptine, brotizolam, bupropion, buspirone, butabarbital, butalbital, capuride, carbocloral, chloral betaine, chloral hydrate, chlordiazepoxide, clomipramine, cloperidone, clorazepate, clorethate, clozapine, codeine, cyprazepam, desipramine, dexclamol, diazepam, dichloralphenazone, divalproex, diphenhydramine, doxepin, estazolam, ethchlorvynol, etomidate, fenobam, flunitrazepam, flurazepam, fluvoxamine, fluoxetine, fosazepam, glutethimide, halazepam, hydrocodone, hydroxyzine, imipramine, lithium, lorazepam, lormetazepam, maprotaline, mecloqualone, melatonin, mephobarbital, meprobamate, methadone, methaqualone, midaflur, midazolam, nefazodone, nisobamate, nitrazepam, nortriptyline, oxazepam, oxycodone, paraldehyde, paroxetine, pentazocrine, pentobarbital, pergolide, perlapine, perphenazine, phenelzine, phenobarbital, prazepam, promethazine, propofol, propoxyphene, protryptyline, quazepam, reclazepam, roletamide, secobarbital, sertraline, suproclone, temazepam, thioridazine, tracazolate, tranylcypromaine, trazodone, triazolam, trepipam, tricetamide, triclofos, trifluoperazine, trimetozine, trimipramine, uldazepam, venlafaxine, zaleplon, zolazepam, zolpidem, and pharmaceutically acceptable salts thereof.

11. The method of claim 10 wherein the first compound is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol, D-tartrate salt.

12. The method of claim 11 wherein the second compound is sertraline.

13. A pharmaceutical composition comprising: (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol or a pharmaceutically acceptable salt thereof; and a second compound selected from the group consisting of adinazolam, allobarbital, alonimid, alprazolam, amitryptiline, amobarbital,

amoxapine, bentazepam, benzoctamine, bromocriptine, brotizolam, bupropion, buspirone, butabarbital, butalbital, capuride, carbocloral, chloral betaine, chloral hydrate, chlordiazepoxide, clomipramine, cloperidone, clorazepate, clorethate, clozapine, codeine, cyprazepam, desipramine, dexclamol, diazepam, dichloralphenazone, divalproex, diphenhydramine, doxepin, estazolam, ethchlorvynol, etomidate, fenobam, flunitrazepam, flurazepam, fluvoxamine, fluoxetine, fosazepam, glutethimide, halazepam, hydrocodone, hydroxyzine, imipramine, lithium, lorazepam, lormetazepam, maprotaline, mecloqualone, melatonin, mephobarbital, meprobamate, methadone, methaqualone, midaflur, midazolam, nefazodone, nisobamate, nitrazepam, nortriptyline, oxazepam, oxycodone, paraldehyde, paroxetine, pentazocrine, pentobarbital, pergolide, perlapine, perphenazine, phenelzine, phenobarbital, prazepam, promethazine, propofol, propoxyphene, protryptyline, quazepam, reclazepam, roletamide, secobarbital, sertraline, suproclone, temazepam, thioridazine, tracazolate, tranylcypromaine, trazodone, triazolam, trepipam, tricetamide, triclofos, trifluoperazine, trimetozine, trimipramine, uldazepam, venlafaxine, zaleplon, zolazepam, and zolpidem, or pharmaceutically acceptable salts thereof.

14. The pharmaceutical composition of claim 13 wherein the (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol is in the form of the D-tartrate salt.

15. The pharmaceutical composition of claim 14 wherein the second compound is sertraline, or a pharmaceutically acceptable salt thereof.